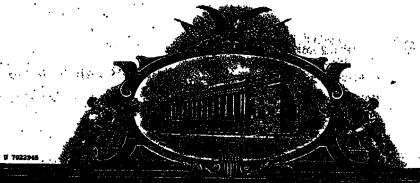
EXHIBIT 5



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July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 5,362,755

ISSUE DATE: November 08, 1994

By Authority of the

Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office

P. SWAIN

Certifying Officer

US005362755A

Barberich et al.

Patent Number: [11]

5,362,755

Date of Patent:

Nov. 8, 1994

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

United States Patent 1191

[75] Inventors: Thursby J. Barberich, Concord; James W. Young, Still River, both of

[73] Assignee: Sepracor, Inc., Mariborough, Mass.

[21] Appl. No.: 163,581

[22] Filed: Dec. 7, 1993

Related U.S. Application Data

Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, [63] Jan. 5, 1990, abandoned.

[51]	Ist. CL ²	A61K 31/135
[52]	U.S. Cl 514	/649; 514/826
[58]	Field of Search	. 514/649, 826

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Primary Examiner-Raymond J. Henley, III. Attorney, Agent, or Firm-Heslin & Rothenberg

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent broachodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

7 Claims, No Drawings

5,362,755

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. 5 No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jun. 5, 1990 now abandoned.

DESCRIPTION

i. Background

Albutzrol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adeayl cyclase, the enzyme which cistalyzes the formation of cyclic-3',5'. Is adeasone monophosphate (AMP) from adenosine triphiosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta-adrenergic receptors to relax amooth muscle tissue, for example, in the bronchial system. Albuterol is 20 most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called cuantioners. Rusnitomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as ensationers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one ensationer may have a specific biological activity while the other ensationer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating broughial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with 45 esthma while minimizing side effects associated with albutered. The method is particularly useful in treating sellims, while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adren-ergic drugs. A composition containing the pure R(--) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dirriness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albaterol can cause teratogenic effects, which are believed to be associated with the 65 S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(--) enantioner of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(--) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from beonchial spasms, abortness of breath) is desired. The optically pure R(--) isomer of abuterol as used herein refers to the isymptotaxy optically pure isomer of all(text-butylamino) methyll-4-hydroxy-m-xylene-a, a'-diol, and to any biologically acceptable salt or exter thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the computation contains at least 90% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the brenchiospanu begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, espenie, solution, canulaion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual desage (quantity administered at a time) and the number of administrations per day will depend on the mode of administra-tion, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about I mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analysis such as aspirine, or an antihistamine or analysis such as aspirine, acctaminophen or Supprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a 5 particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to 10 the drug(s), a liquid carrier and/or propellent. A com-position to be administered in tablet form can include a filler (a.g., lactose), a binder (a.g., carboxymethyl cellu-lose, ginn arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax 15 or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and-/or a coloning agent,

In general, according to the method of the present 20 invention, the optically pure R(--) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to

reduce symptoms of asthma.

The present composition and method provide an 25 effective treatment for astima while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and incressed appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when
the pure isomer is administered. In addition, tenatogenic effects associated with allasterol are believed to reside in the S(+) enantiomer. Thus, administering the pure 35 R(-) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to 40 phen and ibuprofess. ascertain, using no more than routine experimentation,

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many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of recemic albuterol, computing chronically administering to the individual a quantity of an optically pure R(--) isomer of albuterol sufficient to result in broachodilation while simultaneously reducing undesirable side effects, said R isomer being substan-

tially free of its S(+) isomer.

2. A method of cisins 1 wherein the amount of the R(-) isomer of albaterol is greater than approximately

90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(-) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 meg to approximately 90 mog of the R(-) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(-) isomer of albaterol two

to four times daily.

 A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(--) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undestrable side effects and at least one additional drug selected from the group consisting of brouchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is solected from the group consisting of: aspirin, acetamino-

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 5,362,755

: November 8, 1994 DATED INVENTOR(S) : Barbarich et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4.

Line 30, delete the word "or" and insert the word - of -

Signed and Sealed this

Thirtieth Day of September, 2003

JAMES E. ROGAN Director of the United States Patent and Trademark Office

EXHIBIT 6



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office

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July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM: THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 5,547,994

ISSUE DATE: August 20, 1996

By Authority of the

Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office

Certifying Officer

US005547994A

United States Patent [19]

Barberich et al.

[11] Patent Number:

5,547,994

[45] Date of Patent:

Aug. 20, 1996

- [54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL
- [75] Inventors: Thursthy J. Barberich, Concord; James W. Young, Still River, both of Mass.
- [73] Assignee: Sepracos, Inc., Mariborough, Mess.
- [21] Appl. No.: 335,480
- [22] Filed: Nov. 7, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. S,362,735, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jun. 5, 1990, abandoned.

[51] Int. Cl. 6 A61K 31/13S [52] U.S. Cl. 514/649; 514/826 [58] Fleid of Search 514/649, 826

[56]

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Primary Examiner—Raymond Henley, III
Attorney, Agent, or Pirm—Healin & Rothenberg, P.C.

[57]

ABSTRACT

The optically pure R(-) isomer of allowers, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albutrul for treating asthma while minimizing the side effects associated with albuters.

6 Claims, No Drawings

5,547,994

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METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Sec. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Sec. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Sec. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of 15 beta-advenergic compounds. The prime action of beta-advenergic drugs is to stimulate adamy cycles, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. 20 Albuterol acts selectively on beta, advenergic receptors to relax amough muscle tissue, for example, in the broughtal system. Albuterol is most commonly used to treat broachial spismas associated with astisma and is the active component in well-known commercial broachodilators such as Proven-25 til and Ventolin.

The form in which albutered is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Hamiltoners are structurally identical compounds which differ only in that one isomer is a mixtor masse of the other and the mixror images cannot be super-imposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems; one enantioner may have a specific biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albaterol which is active in broachial tissue sufficient 45 to reduce broughtal spenus associated with asthma while tolorishing, side effects associated with albuterol. The method is particularly useful in treating asthma while reduc-ing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is 50 important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of mmy beta-adrenergic drugs. A composition containing the pure R(-) isomer of all outered is particularly useful for this application because this isomer exhibits these desired char- 55 acteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In so children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels recemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure 60 isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(-) exentioner of alboterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimelatory effects and cardine disorders, commonly experienced by albuierol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) emintioner, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from brouchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the leverotatory optically pure isomer of α^1 ((tert-butylamino) methyl] -4-hydroxy-m-xylene-or, of-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) ensutioner" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of alboterol and 10% by weight or less of the S(+) isomer. Optically pure alboterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albeterol is administered to an individual who has asthma. For example, R(-) albeterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albetterol is administered prophylactically, that is, before the broachiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, recially or via an implanted reservoir containing the drog. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual douge (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 meg to about 90 meg of the optically pure R(--) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or symp, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired

In the nethod of the present invention, the optically pure R(--) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiastimatic drug such as theophylline or embutaline, or an antihistamine or analgesic such as aspirin, actaminophen or ibuprofen, can be given with or in close temporal praximity to administration of optically pure, R(--) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albutarol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or 5 propellent. A composition to be administered in tablet form can include a filler (e.g., facture), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a planticizer). A composition to be administered in liquid 10 form can include the combination of drugs and, optionally, an emisifying agent, a flavoring agent and/or a coloring agent,

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in 15 combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousess, shakiness, dizziness and increased appetition and cardiac effects, such as cardiac anythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enamiouner. Thus, administering the pure R(-) jaconer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention

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described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim

Arright Berlings

- 1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of recenic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in brouchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.
- A method of claim 1 wherein the amount of the R(-) isomer of albeterol is greater than approximately 90% by weight,
- 3. A method of claim 2 wherein the amount of the R(-) isomer of alboterol is greater than 99% by weight.
- 4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 meg to approximately 90 meg of the R(-) isomer of abuterol per dose.
- 5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of raccinic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in broachodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of broachodilators, antihistamines and analgesics.
- 6. A method of claim 5 wherein the analgesic is selected from the group consisting of: aspirin, acciaminophen and ibuprofea.

EXHIBIT 7



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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 27: 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM.
THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 5,760,090

ISSUE DATE: June 02, 1998

By Authority of the

Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office

P. SWAIN

Certifying Officer

US005760090A

United States Patent [19]

Barberich et al.

[11] Patent Number:

5,760,090

[45] Date of Patent:

*Jun. 2, 1998

[34] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

[75] Inventors: Timothy J. Barberich. Concord; Jimes W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Mariborough, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5.362,755.

[21] Appl. No.: 691,604

[22] Filed: Aug. 15, 1996

Related U.S. Application Data

[63] Continuation of Sec. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Sec. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,775, which is a continuation of Sec. No. 896,725, Jun. 9, 1992, shandoned, which is a cominuation of Sec. No. 461,262, Jan. 5, 1990, shandoned.

[51] Int. CL⁶ AGIK 31/135 [52] U.S. CL 514/649; 514/649; [58] Field of Search 514/649

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Primary Examiner—Raymond Healey, III
Attorney, Agent, or Firm—Heslin & Rothcaberg, P.C.

[57]

ABSTRACT

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

9 Claims, No Drawings

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METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

This is a continuation of U.S. application Ser. No. 08/335.480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547, 994, which is a continuation of U.S. application Ser. No. 08/163.581 filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which is a continuation of U.S. application Ser. No. 07/896, 725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Ser. No. 07/461.262, filed Jun. 5, 1990, abandoned

BACKGROUND

Abuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyi cyclase, the enzyme which catalyzes the formation of cyclic-3'.5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP fromed mediates the cellular responses. Albuterol acts selectively on beta-adrenergic receptors to relax smooth muscle tissue, for example, in the brouchial system. Albuterol is most commonly used to treat brouchial spasms associated with asthma and is the active component in well-known commercial brouchedilators such as Proventil and Ventolin.

The form in which albutered is presently used is a racemic mixture. That ix, it is a mixture of optical isomers, called coantiomers. Beautiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superinaposed. This phenomenon is known as chirality, Most biological molecules exist as enautiomers and exhibit chirality. Although structurally identical, enautiomers can have profoundly different effects in biological systems; one canastomer may have a specific biological activity while the other canatiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albaterol. The method is particularly useful in treating asthma while reduc-ing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broacho dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albeterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels recemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(--) ensatiomer of albuterol to provide relief from

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invectial disorders, while simultaneously reducing underirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by absterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) examplement, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shormers of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of or [(text-butylamino) methyl 4-hydroxy-m-xylene-ca, ca-diol, and to any biologically acceptable sait or ester thereof. The terms "optically pure" or "substantially free of the S(+) enanticener" as used herein ns that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of abuterol is administered to an individual who has asthma. For example, R(-) albiterol is administered to an individual after onset of arthma to reduce breathing difficulty resulting from asthma. In amother embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the brochiopiasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, 30 intravenously, topically, parenterally, transdormally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the as drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of admi istrations per day will depend on the mode of administration. for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per dry will be adequate in most individuals to produce the desired broachedilation effect. For oral administration, e.g., tablet or symp, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, as antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen. can be given with or in close temporal proximity to administration of optically pure, R(-) abouterol. The two (or more) drugs (the optically pure active iscanes of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a per-ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhabent form can include, in addition to the drug(s), a liquid carrier and/or

propellent. A composition to be administered in tablet form can include a filer (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatia), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid 5 form can include the combination of drugs and, optionally. an emulaifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterel, alone 10 or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthmas.

The present composition and method provide an effective treatment for asthma while minimizing the underirable side effects associated with albeitered use. These side effects includo central nervous system effects, such as tremor. pervousness, shakiness, dizziness and increased appetite. and cardiac effects, such as cardiac anythmia. In children, sido effects, such as excitement, peryousness and 20 hyperkinesia, are reduced when the pure isomer is admin-istered. In addition, teratogenic effects associated with albuteroi are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albeterol.

BOUTVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention

described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma, while reducing side 1. A method of treating asthma, while reducing side effects associated with the administration of raccinic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(-) isomer of abuterol sufficient to result in bronchodilation while simultaneously reducing underirable side effects, said R isomer being substantially free of its S(+) isomer.
2. A method according to claim 1, wherein the albuterol controllers at least 200% by puriotic of the R(-) isomer and not

comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1. wherein the albuterol-compulses at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(-) albutered is administered by inhabition, 5. A method according to claim 4, wherein the optically pure R(-) albutered is administered in an amount of about 30 pg to about 90 pg.

A method according to claim 1, wherein the optically pure R(-) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(-) affortered is administered in an amount of about 1 mg to about 5 mg.

8. A method according to claim 6, wherein the optically pure R(-) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(-) albutered is administered as a syrup.

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EXHIBIT 8



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United States Patent and Trademark Office

July 27, 2006

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U.S. PATENT: 5,844,002

ISSUE DATE: December 01, 1998

By Authority of the

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P. SWAIN

Certifying Officer

United States Patent 1191 Barberich et al.

[11] Patent Number:

Date of Patent:

Dec. 1, 1998

[54] METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY

PURE R(--) ALBUTEROL [75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of

[73] Assignee: Sepracor, Inc., Mariborough, Mass.

[21] Appl. No.: 63,551

[22] Filed: Apr. 21, 1998

Related U.S. Application Data

Continuation of Ser. No. 691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,567,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,262,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abundoned, which is a continuation of Ser. No. 461,262, Jun. 5, 1990, abundoned, which is a continuation of Ser. No. 461,262, Jun. 5, 1990, abundoned, which is a continuation of Ser. No. 461,262, Jun. 5, 1990, abundoned.

Int. Cl. A61K 31/135 is2j v.s. c1. . 514/649; 514/826 [58] Field of Search ... 514/649, 826

[56]

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, ... " Chem. Abstr. 89: 123259m (1978).

Primary Examiner—Raymond Henley, III Attorney, Agent, or Firm-Heslin & Rothenberg, P.C.

ABSTRACT

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

10 Claims, No Drawings

1

METHOD FOR INDUCING BRONCHOBILATION USING OPTICALLY PURE R(-) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/891,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760, 090, which is a continuation of application Ser. No. 08/335, 480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 now U.S. Pat. No. 5,362,755, which is a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jun. 5, 1990, now aban-15 dooed.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3/5-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses.

Albuterol acts selectively on beta-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spassus associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which abuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be super-imposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albutered which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while so minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory officets and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho- 55 dilator and which does not exhibit the adverse side effects of many beta-advenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective 60 method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizzi-ness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-advenergic drugs. In children, side effects such as excitement, nervousness and 65 hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic

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albuterol can cause teratogonic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogonic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albaterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albaterol as used herein refers to the levorotatory optically pure isomer of a [(tert-butylamino) methyl] 4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) countiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albaterol is administered to an individual who has asthma. For example, R(-) albaterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albaterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the deaired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administrated to produce the deaired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drag(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more)

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drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual composads. The composition included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhaltent from can include, in addition to the drug(a), a liquid carrier and/or 10 propellest. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gam arabic, gelatin), an adjuvani, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid 15 form can include the combination of drugs and, optionally, an amulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of allouterol, alone 20 or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of authors.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albaterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, disziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albaterol are believed to reade in the S(+) countiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albaterol.

Bquivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many

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equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim

1. A method of inducing tronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(-) albuterol sufficient to induce said bronchodilation.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

 A method according to claim 1, wherein the optically pure R(-) albuterol is administered by inhalation.

 A method according to claim 4; wherein the optically pure R(-) abuterol is administered in an amount of about 30 µg to about 90 µg.

 A method according to claim 1, wherein the optically pure R(-) albeterol is administered orally.

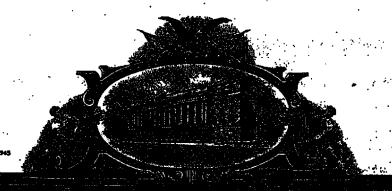
7. A method according to claim 6, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

 A method according to claim 6, wherein the optically pure R(-) albuterol is administered as a syrup.

 A method according to claim 7, wherein the optically pure R(-) albuterol is administered as a symp.

10. A method of inducing bronchodilation or providing relief of bronchospusm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(--) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse

EXHIBIT 9



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United States Patent and Trademark Office

July 27, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 6,083,993 ISSUE DATE: July 04, 2000

By Authority of the

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W. MONTGOMERY Certifying Officer

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United States Patent [19]

Barberich et al.

[11] Patent Number:

6,083,993

[45] Date of Patent:

*Jul. 4, 2000

[54] METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY FURE R(-) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor Inc., Marlborough, Mass.

[*] Notice: This patent is subject to a terminal dis-

[21] Appl. No.: 09/466,107

[22] Filed: Dec. 17, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/200,541, Nov. 25, 1998, which is a continuation of application No. 09/063,551, Apr. 21, 1998, Pat. No. 5,844,002, which is a continuation of application No. 08/691,604, Aug. 15, 1996, Pat. No. 5,760, O90, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,562, 755, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,562, 755, which is a continuation of application No. 07/461,262, Jan. 5, 1990, shundowed.

[51]	Int, Cl.7	-		K 31/13
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[58]	Field of	Search		514/649

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Primary Examiner—Raymond Healey, III
Attorney, Agent, or Firm—Healin & Rothenberg, P.C.

[57]

ABSTRACT

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

17 Claims, No Drawings

6,083,993

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(-) ALBUTEROL

CROSS REFERENCE TO RELATED **APPLICATIONS**

This application is a continuation of our prior copending application Ser. No. 09/200,541, filed Nov. 25, 1998, which is a continuation of application Ser. No. 09/063,551, filed Apr. 21, 1998, now U.S. Pat. No. 5,844,002, which was a 10 continuation of application Ser. No. 08/691,604, filed Ang. 15, 1996, now U.S. Pat. No. 5,760,090, which was a continuation of application Scr. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which was a connation of application Ser. No. 08/163,581, filed Dec. 7, 15 1993, now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-advenergic compounds. The prime action of betaadrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses, Albuterol acts selectively on beta-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial ans associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic 35 mixture. That is, it is a mixture of optical isomers, called emutiomers. Ensutiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most 40 biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enautiomers can have profoundly different effects in biological systems; one ensu-bonier may have a specific biological activity while the

bronchial disorders, such as astimua, in an individual, by 50 administering to the individual an amount of optically pure R(-) albeterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reduc- 55 ing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broachodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizzi- 65 ness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-advenergic drugs.

In children, side effects such as excitement, nervousness and hyperkinesis are reduced when the pure isomer is administered. In addition to the above, at certain levels recemic albuteroi can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albeterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(-) enantiomer of albaterol to provide relief from brouchial disorders, while simultaneously reducing undesirible side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by abbaterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enautionser, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of \alpha^1[(tert-butylamino) methyl]-4-hydroxy-mxylene-a, a'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically re" or "substantially free of the S(+) enantiomer" as use herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is dministered to an individual who has asthma. For example, R(-) albaterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to provent its occurrence or to reduce the extent to which it occurs

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transformally, rectally or via an implanted reservoir containing the drug. The form or via an implanted reservoir containing the drug. The form other enantioner has no biological activity at all, or may neve an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating basis, and will be administered will be determined on an individual basis, and will be absent at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albutered sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the sired broachodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired

> In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmetic drug such as theophylline or terbutaline, or an antihistamine

or analgesic such as aspinin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albutered. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as 5 two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the 10 manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxym- 15 ethyl calluloss, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring 20

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of 25

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetits, and cardiac effects, such as cardiac anythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with 35 albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the terato-genic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described berein. Such equivalents are intended to be as encompassed in the scope of the following claims. to be the a What diclaimed in a white a green

in a patient with the method of treating brouchospasm in a patient with the reversible obstructive airway disease, comprising adminis-精 机焊线电压 化流

tering to said patient a therapeutically effective amount of optically pure R-(-) albeterol.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isome

A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(÷) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(-) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically

pure R(-) albutered is administered orally.

7. A method according to claim 6, wherein the optically pure R(-) albuterol is administered in an amount of about 1 ing to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or

9. A method according to claim 7, wherein the optically pure R(-) albuterol is administered as a syrup,

10. A method of preventing bronchospasm in a patient with reversible obstructive sirvey disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

11. A method according to claim 10, wherein the albuterol

comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

.12. A method according to claim 10, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1%

or less by weight of the S(+) isomer.

13. A method according to claim 10, wherein the optically pure R(-) albuterol is administered by inhalation.

14. A method according to claim 13, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg .

15. Amethod according to claim 10, wherein the optically pure R(-) albutered is administered orally.

16. A method according to claim 15, wherein the optically pure R(-) abouterol is administered in an amount of about 1

mg to about 8 mg.

17. A method according to claim 15, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or